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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/014,335	12/11/2001	Alan R. Fritzberg	295.044US1	1516

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EXAMINER
JONES, DAMERON

ART UNIT	PAPER NUMBER
1616	8

DATE MAILED: 04/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/014,335	FRITZBERG ET AL.	
	Examin r	Art Unit	
	D. L. Jones	1616	

-- The MAILING DATE of this c mmunication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2001 and 24 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *86-105* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *86-105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4 & 7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

ACKNOWLEDGMENTS

1. The Examiner acknowledges receipt of Paper No. 5, filed 12/11/01, wherein the specification was amended; claims 1-85 were canceled; and claims 86-105 were added.

Note: Claims 86-105 are pending.

APPLCIANT'S INVENTION

2. Applicant's invention is directed to compositions and uses thereof wherein the compositions comprise 166-Ho-DOTMP.

101 REJECTION

3. Claim 95 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd. App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

112 REJECTIONS

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 93 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 93 as written is ambiguous because it is a multiple dependent claim that depends upon another multiple dependent claim (e.g., claim 9). Please make the appropriate corrections in order that one may readily ascertain what is being claimed.

6. Claim 95 provides for the use of claim 94, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

103 REJECTIONS

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 86-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Giralt et al (VIIth Int'l Multiple Myeloma Proceedings, Abstract No. 0033, 1999, page 117) ***or*** Giralt et al (Blood, 1999, Abstract #3133, page 709a) **in view** of Bugaj et al (US Patent No. 4,707,353) **in further view of** Kaplan et al (US Patent No. 4,853,209), Bayouth et al (Journal of Nuclear Medicine, 1995,36 (5), 730-737), ***and*** Simon et al (US Patent No. 5,300,279).

Both **Giralt et al** documents disclose 166Holmium-DOTMP in combination with melphalan. The dosage of 166Ho-DOTMP ranges from 20 Gy to 50 Gy. The complex is administered to patients with multiple myeloma. Both documents fail to specifically state that the 166Ho-DOTMP complex further comprise a radioprotectant agent. In addition, the references fail to specifically state that the subject was hydrated.**Bugaj et al** disclose a composition useful for tissue imaging comprising ascorbate, gentisate, or reductate stabilizer in combination with a tin metal or an alloy containing tin useful for in vivo or in vitro skeletal imaging. The compositions may be labeled with technetium-99m or other radioisotopes compatible with skeletal imaging (see entire document, especially, abstract; column 3, lines 57-66). The main objective for adding the stabilizer is so that substantially complete reduction of all the radioisotope added to the formed imaging agent occurs. In addition, the stabilizers allow the radioisotope to remain in the reduced state. The stabilizers may have the further benefit of reducing the formation of labeled impurities which may form during the production and use of the imaging agents (column 5, lines 39-47). Possible stabilizers include ascorbic or gentisic acid (column 5, lines 48-68). Also, Bugaj et al disclose that it is known in the literature that stabilizing compounds such as ascorbic acid may chelate or complex with a radioisotope (e.g., technetium); thus, depositing in soft tissues of the body (column 6, lines 13-20). Optional carriers include using carriers or targeting agents which include phosphonates for skeletal imaging. Preferred skeletal imaging agents include polyphosphonates (column 7, lines 33-68 and 1-38). Bugaj et al disclose a skeletal imaging kit that comprises a diphosphonate carrier, a stabilizer, and optional components. The method

of generating the kit involves adjusting the solution to a pH in a specific range which is dependent upon the particular stabilizer used. The pH is adjusted with any pharmaceutically acceptable acid or base. A kit is generated comprising an ascorbate stabilizer and a carrier/stabilizer solution adjusted to a pH 6.0 (column 11, lines 6-31).

Bayouth et al disclose experiments involving multiple myeloma patients being administered 166Ho-DOTMP (see entire document, especially, abstract). On page 732, column 2 ("Results" section), it is disclosed that both 153Sm-EDTMP and 166Ho-DOTMP. In particular, 152Sm-EDTMP data from a previous cancer metastatic study is disclosed and 16Ho-DOTMP data (see also page 733, Figure 2).

Kaplan et al disclose a composition which may comprise a 166-Ho or Sm-153 radionuclide in combination with a aminophosphonic acid (see entire document, especially, abstract; column 2, lines 18-34; column 3, lines 29-30; and column 12, claim 1).

Simon et al disclose that the administration of compositions comprising a radionuclide such as Ho-166 in combination with an organic aminoalkylenephosphonic acid are useful for alleviating pain and/or inhibiting tumor growth and/or causing regression of tumors and/or destroying the tumor (see entire document, especially, abstract; column 2, lines 31-44). The invention of Simon et al includes therapeutic treatment of primary tumors, invasive tumors, and metastatic bone cancer wherein the neoplasm spreads from other primary sites such as the prostate or breast area.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Giralt et al using the teachings of Bugaj

et al, Kaplan et al, Turner et al, and Simon et al and generate a method of treating bone associated cancer as set forth in Applicant's invention for the following reasons. (1) Both Giralt et al documents indicate that it is well known in the art to use a combination comprising melphalan and 166Ho-DOTMP for studying skeletal cancer. (2) Kaplan et al disclose that holmium-166 is useful radionuclides for in their method of suppressing bone marrow which causes partial or total eradication of the bone marrow. Their method may be used in the treatment of leukemias, lymphomas, myelomas, Hodgkin's disease, and genetic disorders (see column 12, claim 1). (3) Simon et al is made of record because it discloses that the administration of radionuclides (e.g., Ho-166) complexed with an organic aminoalkylenephosphonic acid is a therapeutic way to treat calcific tumors or relieve bone pain (see abstract). In addition, as noted in Simon et al (column 2, lines 31-44) the term calcific tumors as recognized in the art encompasses primary tumors and metastatic bone cancer wherein the neoplasm spreads from other sites such as the prostate and breast. (4) A skilled practitioner in the art would be motivated to combine Giralt et al with Bugaj et al because (a) Bugaj et al disclose a composition comprising a polyphosphonate in combination with a radionuclide and an ascorbate, gentisate, or reductate stabilizer for tissue (e.g., bone) imaging. (b) As indicated by Bugaj et al, the presence of a stabilizer may have the added benefit of reducing the formation of holmium impurities which may form during the production and use of the agent (see column 5, lines 37-68).

A skilled practitioner in the art would recognize based on the teaching of Bayouth et al that when attempting to determine the pharmacokinetics of 166Ho-DOTMP in

urine, subjects should be hydrated during the week they receive the 166-Ho-DOTMP-melphalan combination to accelerate clearance of radioactivity from the renal system (see abstract and page 731, column 2, 'Pharmacokinetics of 166Ho-DOTMP in Urine').

Since each of the references is directed to complexes comprising an polyphosphonate moiety in combination with a radionuclide useful for skeletal imaging, the references may be considered to be within the same field of endeavor. As a result, the references are combinable.

SPECIFICATION

9. The disclosure is objected to because of the following informalities: there are handwritten notes on the side of Table 1 on page 20. Please delete and submit a clean copy of the page to be inserted into the specification.

Appropriate correction is required.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. L. Jones whose telephone number is (703) 308-4640. The examiner can normally be reached on Mon.-Fri. (alternate Mon.), 6:45 a.m. - 4:15 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jose' Dees can be reached on (703) 308- 4628. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

D. L. Jones
Primary Examiner
Art Unit 1616

April 4, 2003